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SYNTHESIS OF 4,5-DIDEOXY-4-*C*-[(*R*,*S*)-PHENYLPHOSPHINYL]-D-RIBO- AND L-LYXO-FURANOSE AND THEIR 1,2,3-TRIACETATES

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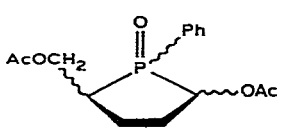
ABSTRACT

2,3-*O*-Isopropylidene-D-ribose diethyl dithioacetal, prepared from D-ribose, was converted in three steps into the corresponding dimethyl acetal, which was monotosylated at O-5, and the ester oxidized at C-4 with pyridinium chlorochromate; addition of methyl phenylphosphinate to the resulting pentos-4-ulose derivative then provided (4*R*,*S*)-4,5-anhydro-2,3-*O*-isopropylidene-4-*C*-[(*R*,*S*)-(methoxy)phenylphosphinyl]-D-*erythro*-pentose dimethyl acetal. Hydrogenation of this compound in the presence of Raney Ni, followed by reduction with SDMA, hydrolysis, and acetylation, yielded the title compounds (seven kinds), the structures of which were established on the basis of their 400-MHz, ^{1}H-n.m.r. and mass spectra. A general dependence of the $^2J_{PH}$ and $^3J_{PH}$ values on the O=P–C–H and P–C–C–H dihedral angles provided an effective method for the assignment of the configurations and conformations of these 4-deoxy-4-phosphinyl-pentofuranoses.

INTRODUCTION

We have previously reported[1] the preparation of 1,5-di-*O*-acetyl-2,3,4-trideoxy-4-*C*-(phenylphosphinyl)-DL-*glycero*-pentofuranose (**1**) as the first derivative of a pentofuranose having phosphorus in the hemiacetal ring, although several *C*-phosphinyl-pentopyranose and -hexopyranose derivatives had already been synthesized[2,3]. Previously, 4-thio-D-ribofuranose had been reported to show novel, biochemical



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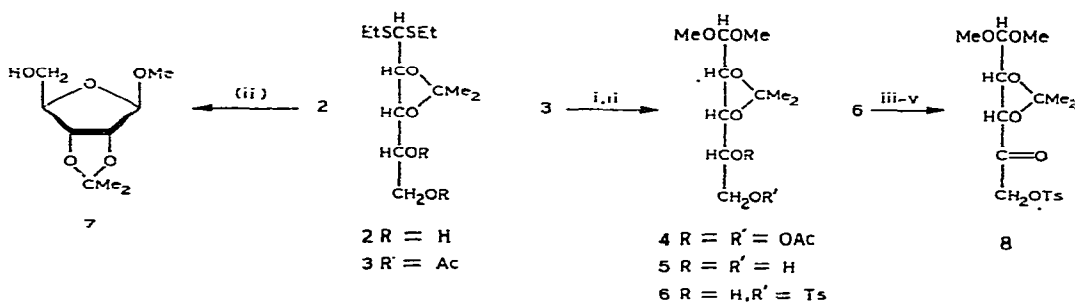
properties[4]. We now describe a new approach to the preparation of 4-deoxy-4-phosphinyl-ribo- and -lyxo-furanose derivatives, starting from D-ribose, and employing a newly developed method of C–P bond-formation.

RESULTS AND DISCUSSION

2,3-*O*-Isopropylidene-D-ribose diethyl dithioacetal[5] (**2**), prepared from D-ribose[6,7], served as the starting material for this synthesis, the diethyl dithioacetal **2** being converted into the corresponding dimethyl acetal (**5**) in an overall yield of 83%. The hydroxyl groups of **2** were first acetylated, and the diacetate **3** was treated with mercuric chloride–cadmium carbonate in absolute methanol[8], to give the dimethyl acetal (**4**), which was deacetylated with sodium methoxide to afford **5**. [An attempted, direct acetal-exchange of **2** (to afford **5**) in the presence of mercuric chloride actually resulted in the formation of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**7**) in 71% yield.] The diol **5** was then converted into the 5-*p*-toluenesulfonate (**6**) in 96% yield. Oxidation of **6** to the pentos-4-ulose **8** was achieved by any of the following methods: (*i*) pyridinium chlorochromate (PCC) with sodium acetate in dichloromethane[9] at 20° (45% yield), (*ii*) PCC with molecular sieves 3A in dichloromethane[10] at 20° (13%), or (*iii*) dimethyl sulfoxide–oxalyl chloride–triethylamine in dichloromethane[11] at −70° (83–90%). Thus, method *iii* was employed for large-scale, preparative work. Compound **8** showed a sharp i.r. absorption at 1750 cm^{-1}, and its ^1H-n.m.r. spectrum was in conformity with the structure (see Experimental).

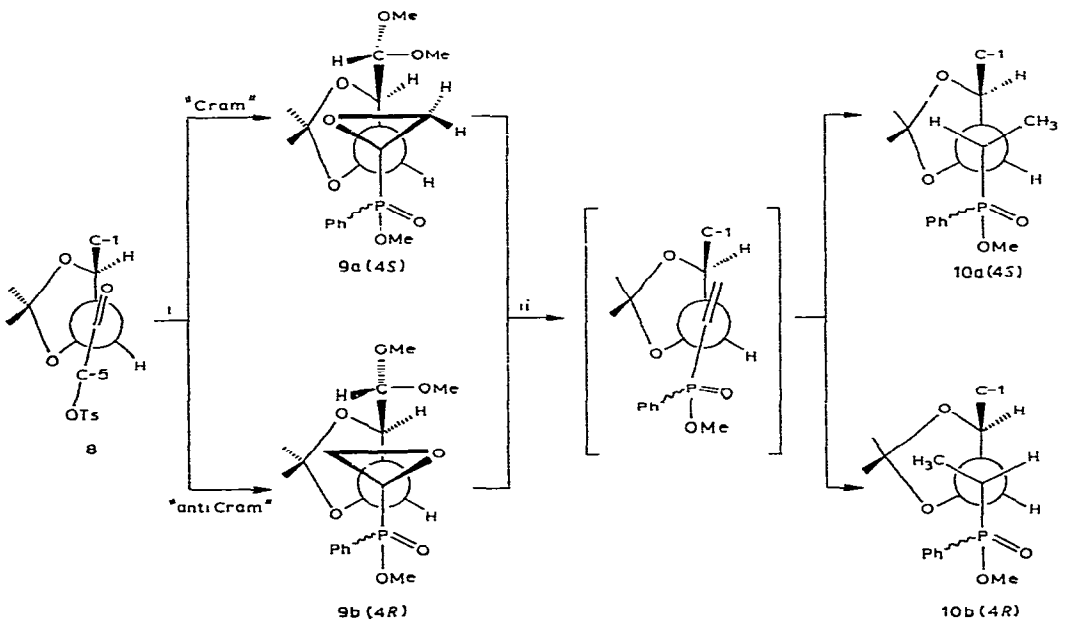
A new, convenient method has been developed[12] for the conversion of 2-oxo-1-*p*-tolylsulfonylalkanes into 1,2-epoxy-1-alkylethanephosphonates by the addition of dimethyl phosphinate in the presence of 1 equiv. of 1,8-diazabicyclo[5.4.0]-undec-



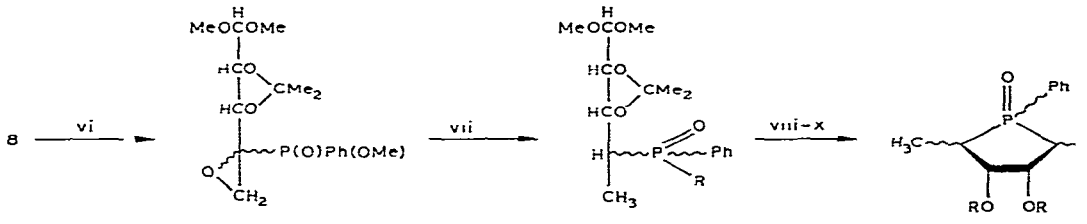
7-ene (DBU), and this procedure was applied for the preparation of (5*R*)- or (5*S*)-5,6-anhydro-1,2-*O*-isopropylidene-5-*C*-(phenylphosphinyl)-α-D-*xylo*-hexofuranoses[13], and these were hydrogenated over Raney Ni, to give 5,6-dideoxy-5-*C*-(phenylphosphinyl)-D-*xylo*-hexofuranose derivatives[14]. According to this scheme, the pentos-

4-ulose **8** was treated with 2 equiv. of methyl phenylphosphinate in the presence of 1.2 equiv. of DBU at room temperature, to give a mixture of (4*R*,*S*)-4,5-anhydro-2,3-*O*-isopropylidene-4-*C*-[(*R*,*S*)-(methoxy)phenylphosphinyl]-D-*erythro*-pentose dimethyl acetals (**9a** and **9b**) in 62% yield, in the molar ratio of 3:7 (after chromatography on silica gel).

The structures of **9a** and **9b** were determined by elementary analysis, and by ^{1}H-n.m.r. spectroscopy, which clearly indicated the presence of the methylene group of the terminal epoxide ring, at δ 2.8–3.4, and the (methoxy)phenylphosphinyl group, at δ ~3.7 and 7.4–8.1. The addition of methyl phenylphosphinate to **8** would be expected to take place in a "Cram" or "anti-Cram" fashion[15], to yield two diastereoisomers with respect to the configuration of C-4; the most likely orientations along the C-4–C-3 bond are illustrated in Scheme 1. Taking into account the deshielding effect of the O atom of the epoxy group to the proximate protons, the slightly downfield shift of the H-1 signal of the minor product (**9a**), and that of the H-2 and H-3 signals of the major product (**9b**), compared with those of the counterparts, led to the tentative assignment of (4*S*) and (4*R*), respectively, for these products. Moreover, the n.m.r. spectra also indicated that **9a** and **9b** consisted of a set of two diastereoisomers with respect to the phosphorus atom, the approximate ratios being 4:3 and 2:1, respectively. Although the anti-Cram type of addition seems to afford the major product **9b**, as was observed in the case of the formation of (5*R*)-5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-[(dimethoxy)phenylphosphinyl]-α-D-*xylo*-hexofu-



Scheme 1. (i) The addition of PhPH(=O)OMe to **8**, and (ii) the catalytic hydrogenation of **9**, with the "Newman" projections along the C-4–C-3 bonds.



vi, $PO(OMe)_2$; vii, H_2—Raney Ni ; viii, SDMA ; ix, H_3O^+ ; x, Ac_2O—C_5H_5N.

ranose[16], the exact configurations of each diastereoisomer could not be decided from the 60-MHz, n.m.r. spectra.

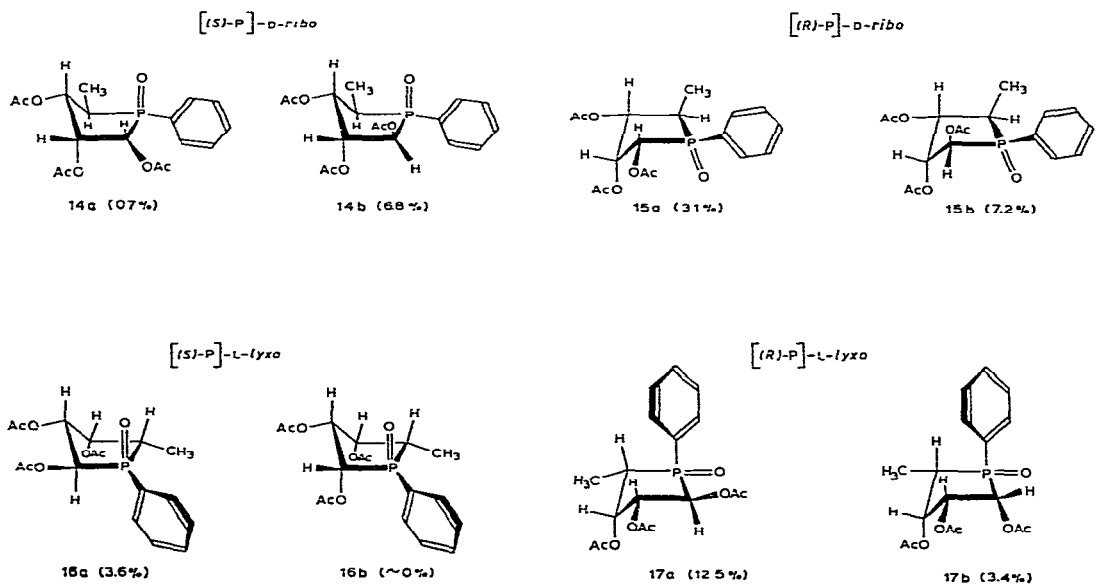
Hydrogenation of **9a** and **9b** over Raney nickel was carried out separately; but, very interestingly, both compounds gave an almost identical mixture of (4*R*,*S*)-4,5-dideoxy-2,3-*O*-isopropylidene-4-*C*-[(methoxy)phenylphosphinyl]-D-*erythro*-pentose dimethyl acetal (**10a** and **10b**) in the molar ratio of 3 : 1 (n.m.r.) with respect to the configuration of C-4. The mixture was separable by t.l.c. on silica gel, and the combined yield was 51%. This result suggests the formation of a common intermediate, such as (4*R*,*S*)-4,5-dideoxy-2,3-*O*-isopropylidene-4-*C*-[(*R*,*S*)-(methoxy)phenylphosphinyl]-D-*erythro*-pentose dimethyl acetal, by deoxygenation prior to the reduction during the hydrogenation, as illustrated in Scheme 1. However, the exact mechanism, as well as the precise assignment of the configurations of C-4 and the phosphorus atom, are uncertain at present.

The next reduction, with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) is known to cause partial epimerization at C-5 in a similar hexofuranose system[17]; nevertheless, the diastereomeric mixture of **10a** and **10b** was subjected to reduction with SDMA, to give a diastereomeric mixture (**11**) of phosphinyl compounds. Because of facile air-oxidation[17,18] mixture **11** was, without isolation, hydrolyzed by refluxing with 0.5M hydrochloric acid, to effect the formation of 4,5-dideoxy-4-*C*-[(*R*,*S*)-phenylphosphinyl]-D-ribo- and -L-lyxo-furanose (**12**), which was expected to be a mixture of the eight diastereomers theoretically possible (with respect to C-1, C-4, and the ring-phosphorus atom). The structural assignment of **12** was made by careful analysis of the 400-MHz, ^{1}H-n.m.r. spectra of the peracetylated derivatives (**13**) obtained by treatment of **12** with acetic anhydride–pyridine. The crude product **13** was separated (by preparative t.l.c. on silica gel, using ethyl acetate as the eluant) into four major fractions, which will be referred to as A, B, C, and D, according to their R_F values.

Fraction C gave a single compound, of m.p. 155–156°, as colorless needles. Although the e.i. mass spectrum of the product gave the highest-mass fragment-ion at *m/z* 326 (1.5%; M — CH_2CO), f.d.m.s. clearly gave the molecular ion at *m/z* 368 ($C_{17}H_{21}O_7P$), corresponding to a tri-*O*-acetyl derivative of **12**. Its structure was

supported by the ^{1}H-n.m.r. spectrum, which consisted of three sharp singlets due to acetyl groups, at δ 1.61, 2.08, and 2.22; a doublet of doublets due to a methyl group at δ 1.28; a complex signal for H-4, at δ 2.5; three remaining ring-proton signals at δ 5.38, 5.51 and 5.70; and a multiplet of the *P*-phenyl group at δ 7.5–7.9, the coupling constants of all signals being determined by employing first-order analysis with the aid of a decoupling technique. The methyl signal appeared at relatively low field, with a slightly small $^3J_{PH}$ (15.1 Hz) and a normal $J_{4,5}$ (7.5 Hz) value, indicating that the methyl group lies close to the oxygen atom on the phosphorus, from analogy with the n.m.r. data for similar, cyclic phosphorus compounds[17–19].

Considering a generally observed feature, namely, that $^2J_{PH}$ is much larger when the coupled proton lies close to the phosphoryl oxygen atom, and is small when remote therefrom[17–19], the small (6.0 Hz) $^2J_{PH}$ value of the H-4 signal of the present product also supported the *cis* relationship of the methyl and P=O group. The proton on C-4 was further coupled to H-3 (δ 5.70, $J_{3,4}$ 4.3 Hz) and H-2 (δ 5.38, $J_{2,4}$ 0.3 Hz). Thus, the remaining signal for a ring proton, at δ 5.51, became assignable to H-1, and the presence of the small $J_{2,4}$ value due to W-coupling suggested the *cis* relationship for H-2 and H-4. A large $^2J_{1,P}$ value (12.1 Hz), and the lack of $J_{1,4}$, indicated that H-1 and the phosphoryl oxygen atom are *cis*. As the absolute configurations of H-2 and H-3 were known, combination of these splitting patterns and the δ values of each signal led to structure **17a**, 1,2,3-tri-*O*-acetyl-4,5-dideoxy-4-*C*-[(*R*)-phenylphosphinyl]-α-L-lyxofuranose, for the product (see Scheme 2). The remarkable difference in the magnitudes of $^3J_{3,P}$ (27.5 Hz) and $^3J_{2,P}$ (~0 Hz) is strongly indicative of an unsymmetrical conformation of the molecule, particularly with respect to H-2



Scheme 2. Structures of 1,2,3-tri-*O*-acetyl-4,5-dideoxy-4-*C*-(phenylphosphinyl)pentofuranoses, and their protable conformations (and yields).

TABLE I

400-MHz, ^{1}H-N.M.R. PARAMETERS[a] FOR 4,5-DIDEOXY-4-*C*-(PHENYLPHOSPHINYL)PENTOFURANOSES IN $CDCl_3$

Compound	*AcO-1*[b] *H-1*	*AcO-2*[b] *H-2*	*AcO-3*[b] *H-3*	*H-4*	*H$_3$-5*	*P-C$_6$H$_5$* {o m p}
14b	2.23[b] s	2.14[b] s	2.12[b] s			7.90 m
	5.15 ddd	5.72 ddd	5.46 ddd	2.67 qddd	1.39 dd	7.58 m
	$J_{1,2}$ 5.7	$J_{2,P}$ 11.7	$J_{3,P}$ 13.5	$J_{4,5}$ 7.5	$J_{5,P}$ 14.2	7.62 m
	$J_{1,P}$ 1.4	$J_{1,2}$ 5.7	$J_{3,4}$ 7.0	$J_{3,4}$ 7.0	$J_{4,5}$ 7.5	
	$J_{1,4}$ 0.5	$J_{2,3}$ 3.8	$J_{2,3}$ 3.8	$J_{4,P}$ 6.0		
				$J_{1,4}$ 0.5		
14a	5.49 dd			2.75	1.30 dd	
	$J_{1,P}$ 11.5				$J_{5,P}$ 14.8	
	$J_{1,2}$ 5				$J_{4,5}$ 7.0	
15a	2.16[b] s	2.23[b] s	2.14[b] s			7.75 m
	5.24 dd	5.92 ddd	5.00 dd	3.01 ddq	0.96 dd	7.58 m
	$J_{1,2}$ 4.6	$J_{2,P}$ 26.6	$J_{3,4}$ 12.3	$J_{4,P}$ 24.0	$J_{5,P}$ 16.5	7.62 m
	$J_{1,P}$ 0.8	$J_{1,2}$ 4.6	$J_{2,3}$ 3.0	$J_{3,4}$ 12.3	$J_{4,5}$ 7.2	
		$J_{2,3}$ 3.0	$J_{3,P}$ 0.5	$J_{4,5}$ 7.2		
15b	2.21[b] s	2.21[b] s	2.15[b] s			7.73 m
	5.29 ddd	5.62 ddd	5.33 ddd	2.90 ddqd	1.06 dd	7.57 m
	$J_{1,P}$ 8.0	$J_{2,P}$ 16.2	$J_{3,4}$ 10.5	$J_{4,P}$ 22.5	$J_{5,P}$ 16.0	7.61 m
	$J_{1,2}$ 3.0	$J_{2,3}$ 3.5	$J_{3,P}$ 6.0	$J_{3,4}$ 10.5	$J_{4,5}$ 7.4	
	$J_{1,4}$ 0.6	$J_{1,2}$ 3.0	$J_{2,3}$ 3.5	$J_{4,5}$ 7.4		
				$J_{1,4}$ 0.6		
16a	5.33 dd	5.75 ddd	5.71	2.75 dqd	0.95 dd	7.90 m
	$J_{1,2}$ 10.5	$J_{2,P}$ 27		$J_{4,P}$ 22	$J_{5,P}$ 16.5	7.6 m
	$J_{1,P}$ 0.6	J 4.5		$J_{4,5}$ 7.5	$J_{4,5}$ 7.5	7.6 m
		J 3.0		$J_{3,4}$ 4.8		
17a	1.61[b] s	2.22[b] s	2.08[b] s			7.72 m
	5.51 dd	5.38 ddd	5.70 ddd	2.50 qddd	1.28 dd	7.56 m
	$J_{1,P}$ 12.1	$J_{1,2}$ 9.4	$J_{3,P}$ 27.5	$J_{4,5}$ 7.3	$J_{5,P}$ 15.1	7.62 m
	$J_{1,2}$ 9.4	$J_{2,3}$ 3.2	$J_{3,4}$ 4.3	$J_{1,P}$ 6.0	$J_{4,5}$ 7.3	
		$J_{2,4}$ 0.3	$J_{2,3}$ 3.2	$J_{3,4}$ 4.3		
		$J_{2,P} \sim 0$		$J_{2,4}$ 0.3		
17b	2.22[b] s	2.28[b] s	2.14[b] s			7.75 m
	5.26 dd	5.40 ddd	5.59 ddd	2.57 qdd	1.36 dd	7.57 m
	$J_{1,P}$ 5.8	$J_{2,P}$ 5.0	$J_{3,P}$ 22.8	$J_{4,5}$ 7.2	$J_{5,P}$ 14.6	7.61 m
	$J_{1,2}$ 3.2	$J_{1,2}$ 3.2	$J_{3,4}$ 5.8	$J_{4,P}$ 6.5	$J_{4,5}$ 7.2	
		$J_{2,3}$ 2.8	$J_{2,3}$ 2.8	$J_{3,4}$ 5.8		

[a]Coupling constants (Hz) confirmed by double resonance. Chemical shifts (δ values) in p.p.m. from Me_4Si. [b]Assignments of acetoxyl groups may have to be interchanged.

and H-3. A few examples have been reported as to the validity of applying the Karplus rule to the relationship between the $^3J_{HP}$ values and the dihedral angles, even in P(V)-heterocyclic systems[20,21]. Thus, the product most probably exists in the E_3 conformation **17a**, wherein the dihedral angles of P–C-4–C-3–H and P–C-1–C-2–H are ~150

and 90°, respectively, resulting in the significant difference in the $^3J_{HP}$ values. At the same time, this shape seems to allow minimization of the nonbonded interactions due to the substituents on the adjacent atoms. Significantly upfield shifts of the H-4, H-2, and AcO-1 signals, and a downfield shift of that of H-3 may be explained in terms of the deshielding and shielding effect of the phenyl ring, the orientation of which is considered to be almost *syn*-parallel to H-3, as illustrated in **17a**. The parameters of the n.m.r. spectrum are recorded in Table I.

The fastest-eluting fraction A also gave a single product as a pale-yellow oil. Careful analysis of its n.m.r. spectrum, as for **17a**, showed the structure **14b**, 1,2,3-tri-*O*-acetyl-4,5-dideoxy-4-*C*-[(*S*)-phenylphosphinyl]-β-D-ribofuranose, for this product. That $^3J_{2,P}$ (11.7 Hz) and $^3J_{3,P}$ (13.5 Hz) have almost the same magnitude suggests an average conformation of ^2E and ^3E (~1:1), wherein the two dihedral angles of P–C-1–C-2–H and P–C-4–C-3–H become close. Apparently, the relatively low energy-barrier between these two forms would result in rapidly interconverting conformations in solution. The assignment of the n.m.r. signals shown in Table I thus seems to be in complete conformity with structure **14b**. The H-1 and H-4 signals appear significantly upfield, indicating the orientation of the *P*-phenyl ring to be almost *syn*-parallel to the AcO-2/AcO-3 region.

The slowest-eluting fraction (D) contained almost the same amounts of two tri-*O*-acetyl derivatives of **12**, which were inseparable by various methods. A similar, n.m.r.-spectral analysis was performed for this mixture, establishing the structures 1,2,3-tri-*O*-acetyl-4,5-dideoxy-4-*C*-[(*R*)-phenylphosphinyl]-α-D-ribo- and -β-L-lyxo-furanose (**15a** and **17b**) in the E_2 and E_3 conformations, respectively, as illustrated in Scheme 2. The assignments of all signals are recorded in Table I, and the chemical shifts and coupling constants of each proton signal are rationalized in terms of the proposed structures **15a** and **17b**. The large values of $^2J_{4,P}$ and $^5J_{2,P}$ for **15a** should be noted, in view of the conformational assignment.

Fraction B was found to be a mixture of three compounds in the molar ratios of 10:5:1. The major product was readily assigned as 1,2,3-tri-*O*-acetyl-4,5-dideoxy-4-*C*-[(*R*)-phenylphosphinyl]-β-D-ribofuranose (**15b**) in an average conformation of E_2 and E_3 in which the former is the more favored, considering that the value of J_{2P} is larger than that of J_{3P} (see Table I). The n.m.r. signals of the two remaining products were not completely clear. Nevertheless, the probable structures 1,2,3-tri-*O*-acetyl-4,5-dideoxy-4-*C*-[(*S*)-phenylphosphinyl]-α-L-lyxo- and -α-D-ribofuranose (**16a** and **14a**) were assigned to the second major and the minor product, respectively, on the basis of their clearly recognizable methyl signals, as well as the H-4 and H-1 values shown in Table I. During the preparative t.l.c., there was observed, between fractions A and B, a very weak band which could have corresponded to the product with the only structure remaining, namely, **16b**, but separation was not attempted because of its negligible amount.

The yields of the eight theoretically possible diastereomers so far established are given in Scheme 2. The β anomers (**14b** and **15b**) preponderate in the formation of the D-ribofuranoses, whereas, for the L-lyxofuranoses, more of the α anomers

(**16a** and **17a**) is produced. This can be rationalized in terms of the thermodynamic stabilities of the anomers of the precursor **12**. The ratio of the combined yields of the D-ribofuranoses (**14a,b** and **15a,b**) to the L-lyxofuranoses (**16a** and **17a,b**) is 9:10, whereas that of the (*S*) to (*R*) isomer of the ring-phosphorus atom (**14a,b**, **16a** to **15a,b**, **17a,b**) is 11:26. A possible explanation for these results is that an almost equimolar (4*R* and 4*S*) equilibration had been reached by the strongly basic SDMA during the reduction of **10**, but the hemiacetal formation from **11** to **12** proceeds more readily for the [(*R*)-phenylphosphinyl]pentofuranoses (**12**), because there is less steric congestion between the *P*-phenyl and the 2- and 3-hydroxyl groups in the precursors of **12**. In fact, a large amount of polar substances remained uneluted by the t.l.c. separation; instead of the intramolecular cyclization to give **12**, intermolecularly condensed, polar products were presumably formed to a considerable extent.

The present work clearly demonstrates effective preparation of 4,5-deoxy-4-*C*-(phenylphosphinyl)-D-ribo- and -L-lyxo-furanose from D-ribose, and also establishes the effective use of ^{1}H-n.m.r. spectra for determining the configurations and conformations of such pentofuranoses.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Silica gel B-5F and C-200 (Wako Pure Chemical Industries, Ltd., Japan) were used for t.l.c. and column chromatography. All reactions were monitored by t.l.c., and products were detected with sulfuric acid–ethanol, or cobalt(II) chloride–acetone, as the indicator. Optical rotations were determined with a Yanagimoto OR-10 polarimeter. I.r. spectra were recorded with a Nihon-Bunko IR-S spectrometer. ^{1}H-N.m.r. spectra for solutions in $CDCl_3$ were recorded with a Hitachi–Perkin–Elmer R-20A (60 MHz) or a Bruker WH-400 cryospectrometer (400 MHz; for compounds **14**–**17**) at 27°. Chemical shifts in p.p.m. are reported relative to tetramethylsilane (δ 0.0) as the internal standard.

2,3-O-Isopropylidene-D-ribose diethyl dithioacetal (**2**). — This compound was prepared from D-ribose in three steps according to Kenner *et al.*[6] and Bukhari *et al.*[7], and was used without purification.

4,5-Di-O-acetyl-2,3-O-isopropylidene-D-ribose diethyl dithioacetal (**3**). — Acetic anhydride (1.38 mL) was added at 0° to **2** (1.57 g) dissolved in dry pyridine (1.87 mL). The mixture was kept for 9.5 h at 20°, diluted with cold water, and extracted with chloroform. The extract was successively washed with cold, 0.5M sulfuric acid, aqueous sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated *in vacuo*, to give **3** (1.79 g, 89%) as a pale-yellow oil; $[\alpha]_D^{26}$ +9.20° (*c* 1.00, $CHCl_3$); ^{1}H-n.m.r.: δ 1.28 (t, 6 H, *J* 7.5 Hz, S-C-CH_3), 1.40, 1.51 (2 s, 6 H, CMe_2), 2.05, 2.09 (2 s, 6 H, OAc), 2.74, 2.76 (2 q, 4 H, *J* 7.5 Hz, S-CH_2-C), 3.89–4.76 (m, 5 H, H-1,2,3,5), and 5.53 (ddd, 1 H, $J_{4,5}$ 6.5, $J_{4,5'}$ 5.5, $J_{3,4}$ 2.0 Hz, H-4).

4,5-Di-O-acetyl-2,3-O-isopropylidene-D-ribose dimethyl acetal (**4**). — The method of Wolfrom and Waisbrot[8] was applied. To a solution of **3** (1.50 g) in absolute

methanol (16.3 mL) were successively added cadmium carbonate (1.97 g) and a solution of mercuric chloride (5.37 g) in absolute methanol (13.3 mL). The mixture was boiled under reflux, with vigorous stirring, for 19 h. The precipitate was filtered off, and the filtrate was diluted with 1 : 1 (v/v) chloroform–water (50 mL), the mixture shaken and separated, and the organic layer repeatedly washed with water, dried (sodium sulfate), and evaporated *in vacuo*. Distillation of the residue gave **4** (1.26 g, 92%) as a pale-yellow oil, b.p. 61–65°/0.08 torr; $[\alpha]_D^{26}$ +31.68° (*c* 1.13, $CHCl_3$); ^{1}H-n.m.r.: δ 1.35, 1.46 (2 s, 6 H, CMe_2), 2.04 (s, 6 H, OAc), 3.35, 3.43 (2 s, 6 H, OMe), 3.89–4.70 (m, 5 H, H-1,2,3,5), and 5.17 (ddd, 1 H, $J_{4,5}$ 6.5, $J_{4,5'}$ 5.0, $J_{3,4}$ 2.5 Hz, H-4).

Anal. Calc. for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55. Found: C, 52.27; H, 7.85.

2,3-O-Isopropylidene-D-ribose dimethyl acetal (**5**). — A few drops of a methanolic solution of sodium methoxide was added to a solution of **4** (198 mg) in absolute methanol (5 mL). The mixture was stirred for 5 h at 20°, the base neutralized by careful addition of Dry Ice, the solution evaporated, the residue mixed with chloroform, and the mixture washed with brine. The organic layer was dried (sodium sulfate), and evaporated *in vacuo*, to give **5** (152 mg, 100%) as a pale-yellow oil; $[\alpha]_D^{26}$ +16.7° (*c* 0.84, $CHCl_3$); ^{1}H-n.m.r.: δ 1.35, 1.44 (2 s, 6 H, CMe_2), 3.49 (s, 6 H, OMe), 3.62 (s, 2 H, OH), and 3.7–4.64 (m, 6 H, H-1,2,3,4,5).

2,3-O-Isopropylidene-5-O-p-tolylsulfonyl-D-ribose dimethyl acetal (**6**). — To a cold solution of **5** (1.80 g) in dry pyridine (7.2 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride (1.54 g) in dry chloroform (3.1 mL). The mixture was stirred for 30 min at 5° and for 5 h at 20°, mixed with a small amount of cold water, and then extracted with chloroform. The extract was successively washed with water, aqueous sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated *in vacuo*, to give **6** (2.84 g, 95%) as a pale-amber oil; $[\alpha]_D^{28}$ +12.75° (*c* 0.91, $CHCl_3$); ^{1}H-n.m.r.: δ 1.28, 1.38 (2 s, 6 H, CMe_2), 2.45 (s, 3 H, S-C_6-CH_3), 3.45 (s, 6 H, OMe), 3.67 (s, 1 H, OH), 3.86–4.53 (m, 6 H, H-1,2,3,4,5), and 7.32, 7.82 (2 d, 4 H, $^2J_{H,H}$ 7.8 Hz, S-C_6H_4-C).

Methyl 2,3-O-isopropylidene-β-D-ribofuranoside (**7**). — Compound **2** (238 mg) was treated with mercuric chloride–cadmium carbonate in absolute methanol as already described. The product, obtained as a pale-yellow oil after the same processing, was[22] **7** (134 mg, 71%); ^{1}H-n.m.r.: δ 1.31, 1.48 (2 s, 6 H, CMe_2), 3.41 (s, 3 H, OMe), 3.58 (dd, 1 H, $J_{5,5'}$ 7.5, $J_{4,5}$ 3 Hz, H-5), 3.69 (dd, 1 H, $J_{5,5'}$ 7.5, $J_{4,5'}$ 1 Hz, H-5'), 4.1 (m, 1 H, OH), 4.37 (dd, 1 H, $J_{4,5}$ 3, $J_{4,5'}$ 1 Hz, H-4), 4.54 (d, 1 H, $J_{2,3}$ 6 Hz, H-3), 4.80 (d, 1 H, $J_{2,3}$ 6 Hz, H-2), and 4.94 (s, 1 H, H-1).

2,3-O-Isopropylidene-5-O-p-tolylsulfonyl-D-erythro-pentos-4-ulose dimethyl acetal (**8**). — The method of Muncuso *et al.*[11] was applied. To a stirred solution of oxalyl chloride (0.16 mL) in dry dichloromethane (3.9 mL) were successively added, at −70° under protection from moisture, a solution of dimethyl sulfoxide (0.27 mL) in dry dichloromethane (0.78 mL), a solution of **6** (726 mg) in dry dichloromethane (1.6 mL) after 5 min, and triethylamine (1.08 mL) after 25 min. The mixture was stirred for 5 min at −70°, allowed to warm to room temperature, diluted with water,

and extracted with dichloromethane; the extracts were combined, successively washed with brine, 1% hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated *in vacuo*, giving **8** (647 mg, 90%) as a pale-yellow oil; $[\alpha]_D^{26}$ −18.5° (*c* 1.05, $CHCl_3$); ν_{max}^{neat} 1750 cm^{-1} (C=O); ^{1}H-n.m.r.: δ 1.34, 1.55 (2 s, 6 H, CMe_2), 2.55 (s, 3 H, S-C_6-CH_3), 3.29, 3.31 (2 s, 6 H, 2 OMe), 4.13–4.85 (m, 3 H, H-1,2,3), 3.80 (s, 2 H, H-5), and 7.38 and 7.85 (2 d, 4 H, 7.8 Hz, S-C_6H_4-C).

Anal. Calc. for $C_{17}H_{24}O_8S$: C, 52.57; H, 6.23. Found: C, 52.68; H, 6.46.

The oxidation of **7** with PCC in dichloromethane in the presence of sodium acetate[9] for 7 days at room temperature afforded a 45% yield of **8**, whereas the same oxidation in the presence of[10] molecular sieves 3 A for 4 days at 20° gave a 13% yield of **8**.

*(4*R,S)-*4,5-Anhydro-2,3-O-isopropylidene-4-*C-[(R,S)-(*methoxy)phenylphosphinyl*]-D-erythro-*pentose dimethyl acetal* (**9a,9b**). — The method of Inokawa *et al.*[13] was followed. To a stirred mixture of **8** (2.53 g) and methyl phenylphosphinate (2.03 g) was added DBU (1.16 mL) at −15°. The mixture was stirred for 27 h at 20°, diluted with chloroform, and saturated aqueous sodium hydrogen carbonate, stirred for 1 day, and the chloroform layer separated, washed with brine, dried (sodium sulfate), and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel using 4:1 (v/v) ethyl acetate–hexane as the eluant, to afford **9a** (46 mg, 19%) and **9b** (102 mg, 43%) both as colorless oils.

Compound **9a**: R_F 0.35 (4:1 EtOAc–hexane); $[\alpha]_D^{22}$ −12.03° (*c* 1.38, $CHCl_3$); ^{1}H-n.m.r.: δ 1.23, 1.45, 1.36*, 1.58* (2 s, 6 H, CMe_2), 2.73, 2.64* (2 dd, 1 H, $^3J_{HP}$ 8, $J_{5,5'}$ 4 Hz, H-5), 3.15, 3.03* (2 dd, 1 H, $^3J_{HP}$ 9, $J_{5,5'}$ 4 Hz, H-5'), 3.35, 3.53, 3.41*, 3.53* (2 s, 6 H, C-OMe), 3.62, 3.82* (d, 3 H, $^3J_{HP}$ 11 Hz, P-OMe), 4.05–4.41 (m, 2 H, H-2,3), 5.05, 5.00* (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), and 7.4–8.1 (m, 5 H, P-Ph); * signals due to the minor isomer (43%) with respect to phosphorus.

Compound **9b**: R_F 0.24 (4:1 EtOAc–hexane); $[\alpha]_D^{24}$ −12.50° (*c* 1.52, $CHCl_3$); ^{1}H-n.m.r.: δ 1.38, 1.46, 1.28*, 1.41* (2 s, 6 H, CMe_2), 2.85, 2.85* (t, 1 H, $^3J_{HP}$ = $J_{5,5'}$ = 5.5 Hz, H-5), 3.30, 3.30* (2 d, 1 H, $^3J_{HP}$ 8, $J_{5,5'}$ 5.5 Hz, H-5'), 3.44, 3.47, 3.39*, 3.44* (2 s, 6 H, C-OMe), 3.80, 3.72* (d, 3 H, $^3J_{HP}$ 11 Hz, P-OMe), 4.45–4.7 (m, 2 H, H-2,3), 4.80, 4.85* (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), and 7.4–8.15 (m, 5 H, P-Ph); * signals due to the minor diastereomer (33%) with respect to P.

*(4*R,S)-*4,5-Dideoxy-2,3-O-isopropylidene-4-*C-[(R,S)-(*methoxy)phenylphosphinyl*]-D-erythro-*pentose dimethyl acetal* (**10a,10b**). — The procedure of Inokawa *et al.*[14] was followed. Thus, **9a** (104 mg) dissolved in absolute ethanol (5 mL) was hydrogenated in the presence of Raney Ni (W-4; 0.5 g) for 46 h. The mixture was diluted with ethanol, centrifuged to remove the catalyst, the supernatant liquor evaporated *in vacuo*, and the residue chromatographed on silica gel (t.l.c.) using 4:1 ethyl acetate–hexane, to give **10a** (38 mg, 39%) and **10b** (13 mg, 14%).

Compound **10a**: R_F 0.33 (4:1 EtOAc–hexane); $[\alpha]_D^{21}$ +11.65° (*c* 0.79, $CHCl_3$); ^{1}H-n.m.r.: δ 1.14 (dd, 3 H, $^3J_{HP}$ 12, $J_{4,5}$ 7 Hz, H_3-5), 1.33, 1.43 (2 s, 6 H, CMe_2),

2.43 (m, 1 H, H-4), 3.35, 3.42 (2 s, 6 H, C-OMe), 3.75 (d, 3 H, $^3J_{HP}$ 10.2 Hz, P-OMe), 4.0–4.8 (m, 3 H, H-1,2,3), and 7.45–8.05 (m, 5 H, P-Ph).

Compound **10b**: R_F 0.15 (4:1 EtOAc–hexane); $[\alpha]_D^{21}$ +16.15° (*c* 1.10, $CHCl_3$); ^{1}H-n.m.r.: δ 1.10 (dd, 3 H, $^3J_{HP}$ 10, $J_{4,5}$ 7 Hz, H_3-5), 1.33, 1.44 (2 s, 6 H, CMe_2), 2.53 (m, 1 H, H-4), 3.35, 3.47 (2 s, 6 H, C-OMe), 3.72 (d, 3 H, $^3J_{HP}$ 10.2 Hz, P-OMe), 3.9–4.65 (m, 3 H, H-1,2,3), and 7.45–8.05 (m, 5 H, P-Ph).

Anal. Calc. for $C_{17}H_{27}O_6P \cdot H_2O$: C, 54.25; H, 7.76. Found: C, 53.82; H, 7.99.

Similar treatment of **9b** (526 mg) with methyl phenylphosphinate gave the same mixture (3:1) of **10a** and **10b** (305 mg, 60%).

1,2,3-Tri-O-acetyl-4,5-dideoxy-4-C-[(R,S)-phenylphosphinyl]-D-ribo- and -L-lyxo-furanose (**13**). — A solution of **10b** (245 mg) in dry toluene (20 mL) was degassed, and then bubbled with argon. To this was slowly added at 0°, under argon, SDMA (70% in toluene, 0.17 mL) which had been further diluted with toluene (2.5 mL), followed by stirring for 10 min; then a small amount of cold water was added at 0° to decompose the excess of SDMA. The mixture was stirred for 30 min, and centrifuged to remove aluminum hydroxide; the precipitate was extracted with several portions of benzene. The organic layers were combined, and evaporated *in vacuo*, giving a quantitative yield of *(4R,S)-4,5-dideoxy-2,3-O-isopropylidene-4-C-[(R,S)-phenylphosphinyl]-D-erythro-pentose dimethyl acetal* (**11**) as a colorless oil.

To product **11**, dissolved immediately in methanol (2 mL), was added oxygen-free, 0.5M hydrochloric acid (12 mL), and the mixture was refluxed under argon for 3 h at 110° (bath), cooled, and the acid neutralized by passing the mixture through a column of (weakly basic) Amberlite IRA-45 ion-exchange resin. The eluate was filtered, and the filtrate evaporated *in vacuo*, to give *(4R,S)-4,5-dideoxy-4-C-[(R,S)-phenylphosphinyl]-D-ribo-* and *-L-lyxo-furanose* (**12**) as a pale-yellow oil (148 mg).

To a solution of crude **12** in dry pyridine (10 mL) was added, at 0°, acetic anhydride (0.6 mL), and the mixture was stirred for 22 h at room temperature. A small amount of water was added, most of the pyridine was removed *in vacuo*, the residue was dissolved in chloroform, and the solution was washed successively with cold 0.5M hydrochloric acid, 5% aqueous sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated *in vacuo*. By preparative t.l.c. using ethyl acetate as the eluant, the residue (157 mg) was separated into four fractions: A, B, C, and D (according to their R_F values); and each fraction was eluted with ethanol.

Fraction A (R_F 0.6) gave **14b** as a pale-yellow oil (17 mg, 6.8%); for 400-MHz, ^{1}H-n.m.r. data, see Table I.

Fraction B consisted of **15b** (18 mg, 7.2%), **16a** (9 mg, 3.6%), and **14a** (2 mg, 0.7%), which could not be separated into single compounds by various methods; R_F 0.5; for ^{1}H-n.m.r. data, see Table I.

Fraction C (R_F 0.35) gave **17a** (32 mg, 12.5%) as colorless needles, m.p. 155–156° (after recrystallization from ethyl acetate–hexane); for ^{1}H-n.m.r. data, see Table I; high-resolution, e.i. mass spectrum: *m/z* (relative intensity): 326 (1.5; $M^+ - CH_2CO$), 268 (8.2), 267 (48), 225 (48), 224 (44), 214 (67), 126 (42), 125 (32), 84

(33), and 43 (100); ^{23}Na-f.d. mass spectrum[25]: *m/z* (relative intensity): 368 (48; M^+) and 279 (100).

Calc. for $C_{13}H_{17}O_4P$ ($M - CH_2CO - CH_2CO_2$): 268.0864. Found: 268.0766.

Fraction D (R_F 0.15–0.3) consisted of a mixture of **15a** (7.8 mg, 3.1%) and **17b** (8.5 mg, 3.4%) which were inseparable by various methods; for ^{1}H-n.m.r. data, see Table I.

Similar treatment of **10a** gave almost the same result.

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